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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,653	12/04/2000	Biaoyang Lin	P-IS 4367	3087

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/27/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,653	LIN, BIAOYANG	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-23 and 25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 9-12 and adds new claims 26-29, which are related to claims 9-12, and are not new matter.

Accordingly, claims 26-29 are examined in the instant application.

The following are the remaining rejections.

OBJECTION

Claims 26-29 are objected to for the use of the language "substantially pure".

Applicant asserts that the specification discloses that the term "substantially pure" means a polypeptide that is substantially free from cellular components or other contaminants present with the polypeptide in nature.

It is noted that term "substantially pure" is defined based on the term "substantially free" which is equally unclear concerning the metes and bound of the term.

REJECTION UNDER 35 USC 101, UTILITY

Claims 26-29 are rejected under 35 USC 101, pertaining lack of a specific and/or well established utility, for reasons already of record in paper No: 16.

Applicant submits a Declaration by Biaoyang Lin, asserting that the Declaration corroborates that the polypeptide of SEQ ID NO:2 is expressed in nature in prostate cells.

Applicant asserts that the use of the polypeptides as immunogens to prepare antibodies and further use of the antibodies to differentiate tissue types such as typing a cell line or tissue of interest, are well established utility. Applicant recites the reference by Weiner et al, and asserts that the antibodies could also be used for immunotherapy.

Concerning specific utility, Applicant asserts that there is no requirement for an absolutely unique specific utility, as an example, a variety of therapeutic agents for treating the same cancer are patented each year, irregardless of the fact that they have a common utility. Applicant requests that the Examiner cites the sources for asserting that a specific utility cannot be shared by several other prostate specific polypeptides.

The submission of the Declaration by Biaoyang Lin, and the recitation of the reference by Weiner et al are acknowledged.

Applicant's arguments in paper No:17 have been considered but are not found to be persuasive for the following reasons:

It is noted that in the Declaration, the detected proteins in the sera of a CaP patient do not seem to have the 151 kDa molecular weight of the PAMP polypeptide (figure 1). Further, since no control sera is shown in figure 1, it is not clear whether the detected proteins in sera are unrelated proteins that cross-react with antibodies against the PAMP polypeptide. Moreover, the detected protein in prostate cell line LNCaP cannot be applied to *in vivo* situation, wherein expression of a gene or protein in cell in

culture cannot be correlated with expression of said gene or protein *in vivo*. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is

recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that, the polypeptide of SEQ ID NO:2 and its variants exist in prostate tissue.

Further, those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide, as overwhelmingly taught by Alberts et al, Shantz et al, McClean et al, Fu et al, and Yokota et al (all of record). Therefore, one cannot predict that the polypeptide of SEQ ID NO:2 and its variants exist in prostate tissues.

In addition, even if the claimed polypeptide is expressed in a prostate specific manner, the use of the polypeptide of SEQ ID NO:2 as immunogens to prepare antibodies is not specific utility, since preparation of antibodies is applied to unrelated polypeptides. Further the particular use of the antibodies specific to SEQ ID NO:2 to differentiate tissue types such as typing a cell line or tissue of interest, and for immunotherapy has not been shown for the particular antibodies specific to SEQ ID NO:2. Therefore, this is a utility which is only potential with respect to the claimed polypeptide. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form.

Moreover, although a specific utility can be shared by for example a certain class of compounds, with related function and structure, the particular specific utility that could be shared by the claimed prostate specific polypeptide and other prostate specific polypeptides has not been demonstrated, and cannot be predicted, because of the great functional and structural diversity of different prostate specific polypeptides.

Further, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, the claimed polypeptide would only serve as the basis for further research . "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a specific and substantial utility that would support the requirement of 35 U.S.C. §101. None of the utilities asserted for the claimed polypeptide meets the three-pronged test of being specific, substantial and credible, according to the guidelines for 35 U.S.C. §101 utility rejection .

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 28-29 are rejected under 35 USC 112, first paragraph, pertaining lack of a clear written description, for reasons already of record in paper No: 16.

Applicant argues that the polypeptides that are at least 90% or 95% identical to SEQ ID NO:2 or to at least specific 350 residues of SEQ ID NO:2 share a common structural attribute of sharing at least 9 out of 10 residues with SEQ ID NO:2 or least specific 350 residues of SEQ ID NO:2. Applicant asserts that Applicant was in possession of the claimed invention.

Applicant's arguments in paper No:17 have been considered but are not found to be persuasive for the following reasons:

It is noted that a polypeptide comprising an amino acid sequence having at least 90% or 95% identical to at least specific 350 residues comprising residues 1075 to 1382 of SEQ ID NO:2 encompass unrelated sequences with unknown structure and length, provided they comprise a fragment which is a 90% or 95% variant with 350 residues comprising residues 1075 to 1382 of SEQ ID NO:2. It is further noted that although the specification discloses that "PAMP polypeptide" means a polypeptide that is structurally similar to human PAMP and has at least one biological activity of PAMP (p.19, second paragraph), the biological activity of PAMP is not disclosed. In addition, it is noted that the specification discloses that a fragment containing residues 1075 to 1382 of SEQ ID NO:2 is not a "PAMP polypeptide" as defined in the specification (p.19, lines 24-27).

The claims encompass variants of the polypeptide of SEQ ID NO:2, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification and all other pending claims do not place any limit on the number of amino acids that could be substituted. Thus the scope of the claims includes numerous structural variants. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could

be deleted or inserted so that the claimed polypeptide could function as contemplated. No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed variants are disclosed, because the function of a polypeptide sequence could be abolished, even with substitution of only one amino acid of the polypeptide (Burgess et al., of record). In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) would be subjected to conservative substitution. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, SEQ ID NO: 2 alone is insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of variants.

For the reasons set forth above and in previous Office action, Applicant is not in possession of polypeptides that are at least 90% or 95% identical to 350 residues comprising residues 1075 to 1382 of SEQ ID NO:2.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

1. Claims 26-29 are rejected under 35 USC 112, first paragraph, pertaining lack of support for a specific and/or well established utility, for reasons already of record in paper No: 16.

The same arguments by Applicant and the reasons for rejection by the Examiner in the above 101 utility rejection apply here as well.

2. Claims 28-29 are rejected under 35 USC 112, first paragraph, pertaining lack of enablement for polypeptides that are at least 90% or 95% identical to 350 residues comprising residues 1075 to 1382 of SEQ ID NO:2, for reasons already of record in paper No: 16.

Applicant argues that the specification teaches the structure of SEQ ID NO:2 as shown in figure 1. Applicant asserts that the specification discloses that the PAMP polypeptides could be prepared from natural sources or produced recombinantly. Applicant asserts that the specification teaches how to make antibodies, that significant PAMP mRNA expression is observed only in the prostate, and that using methods routine in the art, one would be able to identity the tissue type of a sample.

Applicant's arguments in paper No:17 have been considered but are not found to be persuasive for the following reasons:

The specification does not disclose how to make and use variants of a fragment comprising residues 1075 to 1382 of SEQ ID NO:2, which are capable of functioning as that which is being disclosed. The claimed variants would have any type of substitution, deletion or addition throughout the length of the fragment comprising residues 1075 to 1382 of SEQ ID NO:2. Although the methods are routine in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could

function as contemplated. Protein chemistry however is probably one of the most unpredictable areas of biotechnology, and even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein, as overwhelmingly taught by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

February 17, 2003

ANTHONY C. CAPUTA
EXAMINER
TECHNOLOGY CENTER 1600